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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/689,911	10/11/2000	C. Alexander Turner JR.	LEX-0068-USA	9082

24231 7590 06/03/2004

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/03/2004

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 05212004

Application Number: 09/689,911
Filing Date: October 11, 2000
Appellant(s): TURNER ET AL.

David W. Hibler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11 February 2004 (hereinafter, the Brief).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct. The Examiner respectfully disagrees with Appellant's conclusion that the claimed polynucleotide sequences are involved in a number of functions, such as a role in inflammation, for reasons of record and re-stated herein.

(6) Issues

The Appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-8 stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Ohtaki et al. J Biol Chem 274(52): 37041-37045, 1999.

Floren et al. Neuropeptides 34(6): 331-337, 2000.

Skolnick et al. Trends in Biotech 18(1): 34-39, 2000.

Bork, A. Genome Res 10: 398-400, 2000.

Doerks et al. Trends in Genetics 14(6): 248-250, 1998.

Smith et al. Nature Biotech 15: 1222-1223, 1997.

Brenner, S.E. Trends in Genetics 15(4): 132-133, 1999.

Bork et al. Trends in Genetics. 12(10): 425-427, 1996.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. The basis for these rejections are set forth in the previous Office Actions (05 May 2003; 24 September 2002; 01 April 2002) and is also fully set forth below.

Specifically, claim 1 is directed to an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1. Claims 2-3 also recite an isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO: 2

and a nucleotide sequence that hybridizes to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof under highly stringent conditions. Claim 4 is directed to an isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence from amino acid number 33 to amino acid number 141 of SEQ ID NO: 2. Claims 5-8 also recite recombinant expression vectors and a host cell comprising the expression vector.

It is clear from the instant specification that the nucleic acid encoding the novel human protein (NHP) polypeptide has been isolated because of its similarity to known proteins. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate

inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

The specification of the instant application asserts that the NHP polynucleotides and polypeptides share structural similarity with animal galanins and represent new members of the galanin family (pg 2, lines 1-13). The specification teaches that a genomic library can be constructed using DNA obtained from an individual suspected of or known to carry a mutant NHP allele (e.g., a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, an inflammatory disorder, etc.) (pg 8, lines 35-37 through pg 9, lines 1-2). However, NHP's role in obesity, high blood pressure, and inflammation is not specific. For example, does it contribute to inflammation? Does it inhibit inflammation? Also, NHP's role in inflammation is not specific--What kind of inflammation? Infection, autoimmune disease, injury-associated inflammation, etc.? What tissue is NHP expressed in? There is no clear nexus between a specific type or sort of inflammation and a change in amount or form of NHP.

Furthermore, the assertion that the disclosed NHP polypeptides and polynucleotides have biological activities similar to known galanin family members cannot be accepted in the absence of supporting evidence, because the relevant literature reports that structurally, galanin is

unrelated to any known family of neuropeptides or regulatory proteins (Ohtaki et al., pg 37041, 2nd paragraph). Therefore, it is not clear to the skilled artisan what other known galanin family members Appellant is referring to. Floren et al. (Neuropeptides 34(6) : 331-337, 2000) also disclose that considering the diversity in values of receptor affinities for galanin, galanin fragments, and chimeric galanin receptor ligands, it is too early to even classify GALP (pg 335, 3rd full paragraph). The specification also does not disclose any methods or working examples that demonstrate the polynucleotide and polypeptide of the instant application exhibit similar activities of other galanins, particularly human. The skilled artisan would not be able to categorize the polynucleotide and polypeptide of the instant application as a galanin. Additionally, the specification of the instant application does not teach the skilled artisan which domains of the polypeptide of the instant application are structurally characteristic of galanins. One skilled in the art would not know the utility and function of the polypeptide of SEQ ID NO: 2, even if it was a putative galanin protein because, as discussed in the Appellant's response of 08 July 2002 and related art, "galanin is widely distributed in the central and peripheral nervous system where it exhibits a variety of physiological effects (pg 331, Floren et al.) and neither the specification nor the prior art provides for the physiological significance of the disclosed NHP polypeptide.

The polynucleotide and polypeptide of the instant application (SEQ ID NOs: 1 and 2, respectively) are not supported by either a credible, specific and substantial ("real-world") asserted utility or a well-established utility. The polynucleotide and polypeptide do not have a substantial utility because basic research is required to study the properties and activity of the claimed polynucleotide that encodes the polypeptide of SEQ ID NO: 2. The specification of the

instant application does not disclose the function of the polynucleotide and polypeptide and only recites prophetic examples of how the claimed polynucleotide and polypeptide can be utilized in various assays (pg 2-3 and 8-10). It is clear from the instant specification that the polypeptide described therein is what is termed an "orphan protein" in the art. This is a protein whose cDNA has been isolated because of its similarity to known proteins. There is little doubt that, after complete characterization, this DNA and protein, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as NHP, the instant invention is

incomplete. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. Since the instant specification does not disclose a "real world" use for NHP then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claims 1-8 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

A. Do claims 1-8 lack a patentable utility?

Appellant argues at the bottom of pg 4 through the top of page 5 of the Brief that the claimed nucleic acid molecule shares 100% identity at the amino acid level with the first 98 amino acids of a sequence that is described in a journal article by Ohtaki et al. (J Biol Chem 274: 37041-37045, 1999). Appellant asserts that these scientists have functionally characterized human galanin-like peptide (GALP) and given the significant homology between the presently claimed sequence and the human GALP sequence of Ohtaki et al., there can be no question that those skilled in the art would clearly believe that Appellant's sequence is a galanin family sequence, as asserted in the specification as originally filed. Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, according to the Examiner's sequence search of March 4, 2002, the nucleic acid sequence of the instant application has only 69.6% overall similarity to the GALP polynucleotide of Ohtaki et al (please

see attached sequence alignment of Appendix A). The protein encoded by the nucleic acid molecule of Ohtaki et al. has 82% sequence identity with the amino acid sequence of SEQ ID NO: 2 of the instant application (please see attached sequence alignment of Appendix B). Furthermore, although Ohtaki et al. teach that GALP preferentially binds and activates the GALR2 receptor, the function of GALP was not well-established at the time of filing of the instant application because Ohtaki et al. indicate that the physiological significance of GALP should be elucidated in future studies (pg 37041, abstract, 3rd full paragraph; pg 37045). The assertion that the disclosed NHP polypeptides and polynucleotides have biological activities similar to known galanin family members cannot be accepted in the absence of supporting evidence, because the relevant literature reports that structurally, galanin is unrelated to any known family of neuropeptides or regulatory proteins (Ohtaki et al., pg 37041, 2nd paragraph). Therefore, it is not clear to the skilled artisan what other known galanin family members Appellant is referring to. Floren et al. (Neuropeptides 34(6) : 331-337, 2000) also disclose that considering the diversity in values of receptor affinities for galanin, galanin fragments, and chimeric galanin receptor ligands, it is too early to even classify GALP (pg 335, 3rd full paragraph). The specification also does not disclose any methods or working examples that demonstrate the polynucleotide and polypeptide of the instant application exhibit similar activities of other galanins, particularly human. The skilled artisan would not be able to categorize the polynucleotide and polypeptide of the instant application as a galanin. Additionally, the specification of the instant application does not teach the skilled artisan which domains of the polypeptide of the instant application are structurally characteristic of galanins. One skilled in the art would not know the utility and function of the polypeptide of SEQ ID NO:

2, even if it was a putative galanin protein because, as discussed in the Appellant's response of 08 July 2002 and related art, "galanin is widely distributed in the central and peripheral nervous system where it exhibits a variety of physiological effects (pg 331, Floren et al.) and neither the specification nor the prior art provides for the physiological significance of the disclosed NHP polypeptide.

Furthermore, if the NHP polypeptide of the instant application was deemed to be structurally related to galanin or GALP, the state of the art teaches examples of polypeptide families wherein individual members have distinct, and sometimes opposite, biological activities. Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a

common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Based upon the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make the biologically active NHP of SEQ ID NO: 2 without resorting to undue experimentation to determine what the specific biological activities of the NHP polypeptide are.

Additionally, the problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. Certain positions in the amino acid sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions. Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one or ordinary skill in the art to determine, without undue experimentation, the positions in the protein and DNA which are tolerant to change and the

nature and extent of changes that can be made in these positions. Therefore, the regulation and sequestration of the NHP polynucleotide and polypeptide of the instant application are not well characterized and one skilled in the art the art would not find the asserted utility of the NHP polypeptide to be well-established, well-known, specific, or substantial.

Furthermore, in the middle of page 5 of the Brief, Appellant contends that the present situation is analogous to Example 10 of the Revised Interim Utility Guidelines Training Materials. Appellant argues that a rejection under 35 U.S.C. § 101 as lacking a patentable utility and under 35 U.S.C. § 112, first paragraph is not proper when a full length sequence (such as the presently claimed sequence) has a similarity score greater than 95% to a protein having a known function (such as the 100% identity between the claimed sequence and the mature human GALP sequence of Ohtaki et al.). However, Example 10 is inapposite to the facts of the instant case. The polynucleotide sequence in Example 10 of the Utility Guidelines has high homology to DNA ligase encoding nucleic acids. In this example, DNA ligases have a well-established utility in the art based on this class of protein's ability to ligate DNA. However, the polynucleotide and polypeptide of the instant application are not supported by a specific and asserted utility or a well established utility although Appellant asserts that the polypeptide of SEQ ID NO: 2 encoded by the claimed polynucleotide of SEQ ID NO:1 is homologous to the existing GALP protein. However, a function of the NHP of SEQ ID NO: 2 is not demonstrated, and additionally, the function of GALP was not well-established at the time of filing of the instant application. For example, Ohtaki et al. teach that GALP preferentially binds and activates the GALR2 receptor, but that the physiological significance of GALP should be elucidated in future studies (pg 37041, abstract, 3rd full paragraph; pg 37045). Also, the literature discloses many DNA ligases which

have been fully characterized at the structural and functional levels. In the instant case, there is only one similar prior art protein and it has not been fully characterized functionally.

Furthermore, contrary to Appellant's assertion that there is 100% identity between the claimed sequence and the mature human GALP sequence of Ohtaki et al., according to the Examiner's sequence search of March 4, 2002, the nucleic acid sequence of the instant application has only 69.6% overall similarity to the GALP polynucleotide of Ohtaki et al (please see attached sequence alignment of Appendix A). The protein encoded by the nucleic acid molecule of Ohtaki et al. has 82% sequence identity with the amino acid sequence of SEQ ID NO: 2 of the instant application (please see attached sequence alignment of Appendix B). Therefore, there is little doubt that, after complete characterization, the DNA and protein of the instant application, may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete.

At the bottom of pg 5, the first full paragraph at pg 7, the bottom of pg 7, and the first paragraph at pg 9 of the Brief, Appellant asserts that the specification indicates the claimed galanin family sequences are involved in a number of functions, including a role in inflammation (pg 1, line 34). Appellant indicates that galanins have been associated with inflammation and that a mutant NHP allele can result in an NHP-associated phenotype, such as an inflammatory disorder. Appellant also submits that this phenotype is confirmed in genetically engineered mice that lack the murine homolog of the claimed sequence (for example, pg 1, lines 11-15 and pg 2, lines 17-28). Appellant argues that knockout mice had been created in which a portion of the murine homolog of the claimed sequence was deleted. The knockout mice were subjected to a

well-known peritoneal inflammation assay (involving the injection of mice with zymosan). Appellant indicates at the top of page 6 of the Brief that the homozygous knockout animals showed an increase in total white blood cells compared to wild-type control, consistent with, as set forth in the application, the stated role of this protein in inflammation. In the first full paragraph of pg 6 of the Brief, Appellant contends that the broad class of knockout animals lacking the orthologous sequences that correspond to the claimed sequence are clearly supported in the specification. Appellant also points out that the fact that the specification does not specifically single out knockout mice is irrelevant to the utility issue at hand.

Appellant's arguments have been fully considered but are not found to be persuasive. Although Appellant asserts that the claimed polynucleotide is involved in a number of different functions, such as inflammation (as evidenced by knockout mice), this assertion is not specific or substantial. The specification does not disclose a correlation between any specific disorder and an altered level or form of the NHP polypeptide encoded by the claimed polynucleotide. In order for a polynucleotide or polypeptide to be useful, as asserted, for diagnosis or treatment of a disease, there must be a well-established or disclosed correlation or relationship between the polynucleotide or polypeptide and a disease or disorder. Also, the specification does not teach any specific diseases or conditions (particularly inflammation) that are associated with a mutated, deleted, or translocated gene of the instant application (SEQ ID NO: 1). For example, does NHP play a role in inflammation associated with infection, injury, autoimmune disease, etc.? Significant further experimentation would be required by the skilled artisan to identify such a disease or condition in a subject, as well as the specific tissues or cells that are involved. Since this asserted utility is also not present in mature form so that it could be readily used in a

real world sense, the asserted utility is not substantial. Furthermore, the specification does not specifically disclose any methods or working examples as to the generation of knockout mice lacking the murine homolog of the claimed polynucleotide. The specification also does not disclose subjecting the knockout animals to intraperitoneal inflammation assays to assess the immune system challenge with zymosan. The specification only teaches that "transgenic animals that express a NHP transgene, or "knockouts" (which can be conditional) that do not express a functional NHP" can be generated (pg 2, lines 26-28). Also, the knockout mouse evidence is not commensurate in scope with the broadly asserted utility that NHP plays an undefined role in an unspecified inflammatory response. It is noted that Appellant has not brought forth any evidence or results during the prosecution of the instant application regarding assays that may have been performed with knockout mice.

In the last paragraph at pg 6 of the Brief, Appellant states that the zymosan assay is well known to those of skill in the art, having been in use for over 20 years, and cites Barrios et al., Am J Pathol 99 : 731-740, 1980 (abstract). Appellant states at the top of pg 7 that a patent need not disclose what is well known in the art. At pg 7-8 of the Brief, Appellant cites pertinent case law reviewing the legal standard of utility. The Examiner acknowledges that Barrios et al. teach an experimental model of hypersensitivity pneumonitis induced by zymosan in New Zealand white rabbits. However, as discussed above, the specification of the instant application does not disclose a correlation between any specific disorder or condition and an altered level or form of the NHP polypeptide encoded by the claimed polynucleotide. In order for a polypeptide to be useful, as asserted, for diagnosis or treatment of a disease, there must be a well-established or disclosed correlation or relationship between the polypeptide and a disease or disorder. The

specification also does not disclose the generation of NHP knockout mice or their subjection to the peritoneal inflammation assay. Although a patent need not disclose what is well-known in the art, the instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potentially practical uses of the polypeptide encoded by the claimed polynucleotide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Additionally, at pg 8-9 of the Brief, Appellant further argues that the claimed nucleic acid sequence has utility in assessing gene expression in a DNA array or gene chip, and cites several issued U.S. patents covering the gene chip technology. Appellant also contends that as the present sequences are markers of human chromosome 19, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would recognize that the nucleotide sequences would be an ideal, novel candidate for assessing gene expression using DNA chips. Appellant includes a discussion of the financial success of using DNA chips by such companies as Affymetrix, GeneLogic, ABI-Perkin-Elmer, HySeq, Rosetta Inpharmatics and Incyte. At pg 9 of the Brief, Appellant states that nucleic acid sequences are commonly used in gene chip applications without any information regarding the function of the encoded protein. Appellant adds that expression profiling does not require knowledge of the function of a particular nucleic acid on the chip. Appellant's arguments have been fully considered but are not found to be persuasive. First, Appellant mischaracterizes the Examiner's

position as requiring Appellant to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications. The biological role of a polynucleotide or encoded protein is not required to render a gene chip marketable and is currently being exploited by a number of companies to determine correlations between expression patterns of nucleic acids and diseases. The Examiner would like to draw the Board's attention to the definition of the terms "a gene chip" mentioned in the Brief (pg 8, 1st paragraph; pg 9, last sentence of 2nd paragraph) and in the instant specification (pg 5, lines 1-4) by the Appellant. A gene chip is a customized device in biomedicine that allows researchers to detect, simultaneously, the presence and activity patterns of tens of thousands of DNA sequences. A gene chip can be used by researchers to describe the genetic malfunction associated with a disease, detect the presence of the disease in a particular patient, calculate a patient's genetic predisposition to that disease or identify the medicines likely to be most effective in treating a particular patient with the disease. A correlation is required between altered expression of a nucleic acid and a particular disease or disorder; otherwise experimentation is required to determine what genes are altered in which diseases. Even if the expression of Appellant's individual polynucleotide is affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what use any expression information regarding this polynucleotide could be put.

At page 9 of the Brief (first full paragraph), Appellant points out that the claimed nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequences has been identified, as have tissues of interest, as in the present case, and that once the role of the particular nucleic acid is known, the level of gene expression has an even greater significance. Appellant asserts by identifying the physiological role of the claimed sequence, specifically of the claimed sequence in inflammation, the claimed sequence has a far greater utility in gene chip applications than just any random piece of DNA. Appellants' arguments have been fully considered but are not deemed persuasive for the following reasons. The instant specification and Brief assert that the nucleic acids of the instant invention are homologous to galanin and play a role in inflammation. It has not been established that the claimed nucleic acid sequences are expressed at altered levels or forms in a specific diseased tissue as compared with the corresponding healthy tissue. Also, NHP's role in inflammation is not specific or substantial. One skilled in the art does not know if the polynucleotide and polypeptide contribute to inflammation or inhibition of inflammation. The skilled artisan does not know what kind of inflammation NHP is involved in. For example, infection, autoimmune disease, injury-associated inflammation, etc.? What tissue is NHP expressed in? There is no clear nexus between a specific type or sort of inflammation and a change in amount or form of NHP. If the claimed nucleic acid molecules were in a gene chip and a compound caused decreased expression of the claimed nucleic acids, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to acerbate an unspecified disease? If it had been disclosed that the claimed nucleic acids are expressed at a higher level in a particular diseased tissue as compared with the corresponding healthy tissue, then the skilled

artisan would infer that a compound that decreased expression of the nucleic acid molecule might be a good drug candidate that targets the disease. However, such would still require substantial further experimentation and it is not the case here. In addition, the claimed nucleic acid molecules may very well be expressed at equivalent levels in healthy tissues. If that were the case, then the compound would not be a good drug candidate. The claimed nucleic acid molecules may also very well be expressed at a lower level in a particular diseased tissue as compared to the corresponding healthy tissue. In this situation, a compound that decreased expression of the claimed polynucleotides would *not* be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed nucleic acid molecule as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed nucleic acid molecules (or proteins encoded by the nucleic acids) and any diseases or disorders, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Thus, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

There is no doubt that a gene chip (or DNA chips) is a valuable tool in gene expression monitoring and drug discovery. However, the claims are not drawn to the technique, but rather to nucleic acid molecules which have not been disclosed as being associated with any particular diseases or conditions by its being expressed at an altered level or form in a specific diseased tissue as compared to the corresponding healthy tissue. Any nucleic acid molecules could be added to a gene chip. The use of the claimed uncharacterized nucleic acid molecules in such

studies would have provided no more beneficial information than the use of any other unidentified nucleic acids. Thus, this asserted utility is not specific. Determining the relationship between the claimed nucleic acid molecules and any specific diseases or disorders would require significant further research. Therefore, this asserted utility is also not substantial.

Additionally, at pg 10-11 of the Brief, Appellant argues that the Examiner has confused the requirement for a specific utility with an alleged need for a "unique" utility. Appellant argues, citing case law, that the fact that other expressed sequences could be used to track gene expression patterns on a gene chip, or the fact that a small number of other nucleotide sequences could be used for gene mapping to map the protein coding regions in this specific region of chromosome 19, does not mean that the uses of the present sequences are not specific utilities. Appellant cites Carl Zeiss Stiftung v. Renishaw PLC, 945 F.2d 1173, 20 USPQ2d 1094 (Fed. Cir. 1991) which sets forth that "an invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications". However, Carl Zeiss is inapposite to the facts of the instant case. In Carl Zeiss, the district court had found that a claim to a probe containing a stylus which is mounted to a movable arm above a table which supports an object to be measured lacked utility because "the arbitrary presentation of part of an invention does not constitute a claim of a valid invention" and that the claimed device could not function as a probe. See Carl Zeiss at 1180. In the instant case, the claims lack utility not because they are incomplete, and not because they do not set forth the best or only way to accomplish a result, and not because they are not unique, but because they do not have either a well-established utility or a specific and substantial asserted utility. First, Appellant is mischaracterizing the Examiner's position regarding the requirements for a specific utility. There

is no dispute on the case law itself. The issue at dispute is what constitutes a specific utility. A specific utility is a utility specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. To satisfy the utility requirement under 35 U.S.C. § 101, a utility does not need to be unique; however, it must be specific. The use of the present nucleic acid in tracking gene expression patterns on a gene chip is not specific, because such a use would be applicable to any nucleic acids. Secondly, it is noted that Appellant fails to specifically disclose the use of the present nucleic acid sequences in mapping the protein coding regions (5 coding exons of the gene encoding SEQ ID NO: 1) in chromosome 19 in the specification as filed. Appellant only starts to make this specific argument in this Brief and the specification has not asserted any utilities relevant to this property. This asserted utility is not specific or substantial. The specification has not asserted any utilities relevant to this property and such assays can be performed with any polynucleotide. Further, the specification does not disclose a specific DNA target. The asserted patentable utility of a chromosomal marker or to detect chromosomal aberrations for the claimed NHP nucleic acid molecules is not substantial because one skilled in the art would not readily use the nucleotide sequences since they are not associated with a specific disease-related gene. As noted above and in the final rejection, such uses are all considered research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. Thus, all asserted uses are not specific and substantial.

It is further noted that the patents on batteries, automobile tires, golf balls, and treatments for a variety of human diseases are issued by the USPTO because the invention in each patent has a specific and substantial utility, not simply because the claimed subject matter is related to

batteries, automobile tires, golf balls, or disease treatment. For example, a golf ball has a specific feature that makes the ball fly higher and further away as compared with other balls; a compound has a particular property that can be used to treat a specific disease, e.g., prostate cancer. Such is not the case here.

Additionally, Appellant asserts that billions of dollars have been invested in the human genome project, resulting in useful genomic data. Appellant newly cites Venter et al. (Science 291: 1304, 2001) and Jasny and Kennedy (Science 291: 1153, 2001) to allegedly demonstrate the significance of expressed sequence information in the structural analysis of genomic data (pg 11, first full paragraph of the Brief; pg 12, the bottom of the second paragraph of the Brief). It is noted that these references were not included with the Brief or provided in any previous communications from Appellant. Therefore, they have not been considered by the Examiner. First, commercial success is not one of the requirements for utility under 35 U.S.C § 101 nor is it relevant to utility. Many items enjoy commercial success without having utility, such as pet rocks. The Examiner is not disputing that one of skill in the art can see the potential usefulness of information coming out of the human genome project. However, it is also known in the art that this information is valuable to the extent that it provides a starting point for scientists to further investigate the biological significance of the genetic information collected and possibly discover how to treat many conditions and diseases. In fact, while the potential usefulness of human genomic data was enormous, the lack of an immediate use for human genomic data was the primary reason why it was the federal government and not a private entity who first provided funding for the Human Genome Project. While it is agreed that the disclosure of an additional human NHP polynucleotide provides more information in regard to the human genome, in the

absence of any additional information in regard to any property other than its sequence, the isolation of the human polynucleotide of the instant application is only useful as a starting point for researchers to further investigate its biological significance, therefore the utility of the instant polynucleotide, as clearly stated in MPEP § 2107.01 is not a "real world" substantial utility.

Beginning at the second full paragraph at pg 11 through the top of pg 12 of the Brief, Appellant asserts that the present nucleotide sequence has a specific utility in determining genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions. Appellant states that this is evidenced by the fact that SEQ ID NO:1 can be used to map the 5 coding exons on human chromosome 19 (present within Genbank Accession No. AC024580). Appellant submitted an alignment for AC024580 (Exhibit B). Appellant argues that the claimed polynucleotide sequence provides biologically validated empirical data and that sequences can be used to design primers for use in amplification assays to detect mutations within exons, introns, and splice sites. Appellant argues that the present polynucleotide provides specificity in localizing to the specific region of human chromosome 19 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences.

This has been fully considered but is not deemed to be persuasive because such a utility is considered a research utility only designed to identify a particular function of the claimed sequences and is not a substantial utility. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." While the Examiner agrees with the Appellant on the scientific value of the claimed polynucleotide sequences and on the significance of expressed sequence information in structural analysis of

genomic data, such a use of the polynucleotide sequences in gene mapping does not represent a specific and substantial utility. It is noted that the specification has not asserted any utilities relevant to this property and one skilled in the art would not readily use the nucleotide sequences since they are not associated with a specific disease-related gene. Exhibit B and Venter et al. merely show the significance of expressed sequences in the structural analysis of genomic data; they do not show that the present polynucleotide sequences have a patentable utility.

Beginning at the second paragraph at pg 13 of the Brief, Appellant summarizes case law on the utility requirement and urges that the present claims clearly meet the requirement of 35 U.S.C. §101. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility. Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, the statement, "(t)o violate §101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The claimed invention in the instant case is drawn to nucleic acid sequences, not a device; the instant rejection under 35 U.S.C. §101 is not directed to inoperativeness of a device, rather to a lack of patentable utility of the claimed nucleic acid sequences; and the instant issue is whether the asserted utilities meet the three-pronged test for a patentable utility. Furthermore, *In re Brana* (34 USPQ2d 1436 (Fed. Cir. 1995), as stated by Appellant, is concerned mainly with the utility of *pharmaceutical compositions* whereas the present invention is concerned with the utility of galanin *proteins.* Appellant makes no mention in the arguments of *Brana* that the compounds, themselves, to be used in the pharmaceutical

compositions do not have utility. Appellant only states that *Brana* is concerned with the *pharmaceutical compositions* comprising these compounds. Appellant discusses the significance of the FDA and Phase II testing regarding *Brana*. However, these issues are not relevant in this situation. If Appellant was claiming that the protein of the present invention, or nucleic acids encoding these proteins, could be used in pharmaceutical compositions, that may be considered analogous. However, the proteins themselves would first need to possess utility in order for the pharmaceutical composition to possess utility. Since the proteins of the present invention do not possess utility, any comparison to *Brana* is, respectfully, irrelevant. As stated on page 5-6 of the Office Action dated 9/24/04, a patent is not a hunting license. This same statement can be made with regard to Appellant's argument using *In re Angstadt and Griffin*. Appellant states that "the need for some experimentation does not render the claimed invention unpatentable" (bottom of page 14 of the Brief). However, the case law only refers to enablement, not utility. Some amount of experimentation is acceptable under 35 U.S.C. § 112, first paragraph. For example, optimization of drug dosages is considered routine experimentation, not undue. However, in the instant case, significant further research is required to determine what role NHP plays in what sort of inflammation or any other function of NHP. This is not a routine matter of optimization, rather, it is the establishment of a basic correlation. The invention is based on only what is disclosed in the specification. The instant specification is that the protein is believed to be a galanin protein, with no further support of utility.

Furthermore, while the FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, and the requirement for the utility of the claimed invention is different from the FDA standard for drug approval, 35 U.S.C. § 101 does require a

specific, substantial, and credible utility, or well-established utility for an invention. Such a utility has to be a "real world " context of use which does not require significant further research. Appellant confuses this requirement with the "further research and development" needed in pharmaceutical composition and drug development. In other words, a patentable utility has to be clearly identified or immediately apparent in the specification, whereas some "further research and development" is permitted in drug development. For example, determining optimal dosages or drug tolerance in human is further research and development, which is acceptable under 35 U.S.C. § 101 because it is not significant. On the other hand, determining a specific disease to be treated by a drug constitutes significant further research and development, which is not acceptable under 35 U.S.C. § 101.

Secondly, since the specification fails to disclose a specific, substantial utility or a well-established utility, the present claims do not satisfy the utility requirement of 35 U.S.C. §101. Merely citing case laws on the utility requirement does not constitute a patentable utility for the present invention.

In the instant case, the specification fails to disclose the biological functions, physiological significance, or any specific and substantial utility of the claimed molecules. Without such information, one in the skilled art cannot use the claimed invention in a meaningful manner. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

It is further noted that the instant application was filed October 11, 2000. No evidence on the specific biological functions or physiological significance of the molecules of the present

invention has ever been brought forth in an appropriate form during the prosecution history. This supports the Examiner's position that significant further research or undue experimentation is required to identify such information.

Finally, at pages 15 of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines and the validity of issued U.S. patents. The Examiner has no authority to comment on the legality of the Guidelines and the validity of U.S. Patents. However, the current rejection is in compliance with the most currently-published version of the Utility Guidelines which require that all biological inventions must have credible, specific and substantial ("real world") utility. Additionally, each Patent Application is examined on its own merits. The invention that was deemed allowable in one patent has no bearing on this application.

For the above reasons, it is believed that the rejections should be sustained. Appellant's arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the *prima facie* case of lack of utility and it is believed that the rejections should be sustained.

B. Are Claims 1-8 Unusable Due to a lack of Patentable Utility?

As Appellant indicates at page 16 of the Brief, a rejection under U.S.C. § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 35 U.S.C. § 101.

Therefore, for reasons set forth above, Appellant's arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the *prima facie* case of lack of utility.

For the above reasons, it is believed that the rejections should be sustained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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